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PhRMA

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 02D-0002; Comments on "Draft Guidance for Industry on Developing Drugs to Treat Inhalational Anthrax (Post-Exposure)"; 67 *Federal Register* 12021, March 18, 2002

Dear Sir/Madam:

The following comments on the above Draft Guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over $30 billion in the discovery and development of new medicines.

Importantly, PhRMA members have played an important role in responding to the threats of bioterrorism. This draft guidance describes a part of the regulatory framework that will enable us to continue to contribute to this important area of domestic security and health. PhRMA welcomes this draft guidance on FDA's current thinking on development of drugs for post-exposure treatment of inhalational anthrax. Comments were prepared by PhRMA's Antimicrobial Working Group, consisting of scientific, medical, and regulatory representatives from the majority of member companies who sustain research, development, and manufacturing efforts for antimicrobial drug products. These comments are offered in the spirit of constructive dialogue in the interest of maximizing the utility of this guidance and, importantly, speeding development of products to combat bioterrorism pathogens. PhRMA's Antimicrobial Working Group would be pleased to discuss any of these comments with FDA, at the Agency's request.

General Comment

PhRMA suggests that the draft guidance be revised to recognize the circumscribed role of industry in developing antimicrobials for inhalation anthrax. There are many practical limitations for conducting the types of microbiology and animal studies outlined in the guidance. Clearly, this is a collaborative effort of government and industry to develop new agents against anthrax and other bioterrorism pathogens. Hence, the title of the

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document should delete the phase "for Industry"; much of the effort for anthrax depends directly upon government facilities (especially around animal models) to meet FDA criteria.

All stakeholders recognize that very few laboratories are ready and able, today, to perform the *in vitro* and *in vivo* studies described in the draft guidance. Further, PhRMA expects few new laboratories will be established to acquire such testing capabilities because of the increasing legal, regulatory, and security concerns about the biohazard posed by *B. anthracis* and other pathogens with biological weapons potential. There is justifiable concern at the local, state, and federal levels about the safe storage, use, and security-containment of *B. anthracis*. Under current conditions, it would seem that a centralized, standardized testing site and facility under government authority (with all appropriate security) may be best suited to conduct the *in vitro* and *in vivo* testing suggested in the draft guidance, as well as collaborate on the development of animal models in smaller species (which may be a safer alternative to the rhesus monkey model). It would be helpful if FDA would comment on the acceptability of conducting studies, particularly *in vivo* studies, at those offshore facilities (e.g., in certain European countries) that may be appropriately designed and licensed to handle bioterror pathogens. PhRMA encourages FDA to collaborate with industry, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), CDC, and others to assure that the current very limited capacity of secure laboratories to study *B. anthracis* does not continue to limit our collective ability to evaluate the efficacy of drugs for treatment of inhalational anthrax.

Page 1, Introduction: While it makes sense to limit this guidance to currently marketed products, the agency should include some phrasing with regard to consideration of new or novel agents. This will become increasingly important, in light of potential bioterrorism threats with genetically modified pathogens. The use of newer, less established (less post-marketing information), but highly active antimicrobial agents should be made possible within the guidance.

Page 3, Section C, Microbiology: The lack of standardized methods for performance and interpretation of susceptibility testing of *B. anthracis* continues to impair progress in this field. The guidance should more specifically note that discrepant results are obtained in susceptibility testing, depending on the methodology used. While the guidance acknowledges that the suitability of the current NCCLS broth dilution testing method for susceptibility testing of drugs against *B. anthracis* is under evaluation by the FDA, CDC, and NCCLS, it is not clear if the current NCCLS methodology would be acceptable to the FDA in the interim. The guidance should provide a clearer endorsement of methodology such that *in vitro* work performed by the sponsor will be acceptable to the FDA.

Additionally, the FDA should incorporate any available *in vitro* data in an attachment to this draft guidance so that the document is as grounded as possible in the data pertaining to known or potential bioterrorism isolates (although, again, the discrepancies between different methods should be noted). Any available information on resistance of these isolates to penicillin, doxycycline, ciprofloxacin, or other drugs should be included.

Page 4, Section III (line 191): The paragraph "Antimicrobial Pharmacokinetics" requests that sponsors show good agreement between Cmax and Cmin in monkeys and humans. More language should be included in the document on the use of PK/PD parameters to assess susceptibility and resistance. The government should support more work in this area to determine the "target" PK/PD parameters that would predict efficacy. Appropriate small animal data should play a role in defining these parameters and should be accepted by the agency.

Page 5, Section III (line 220): The draft guidance mentions the need for "evidence of safety up to and exceeding 60 days". Does this mean preclinical data or clinical data? The document mentions that sufficient safety data on prolonged drug dosing in humans should be available (line 487). It is unlikely that there will be 60-day dosing data in humans for many antibiotics; possible alternatives should be supplied.

Page 7, Section A (lines 286-301): The draft guidance suggests that labeling for *B. anthracis* can only be obtained when a sponsor submits an application to report results of *in vitro* studies, an *in vivo* study in the rhesus monkey model of inhalation anthrax, and other supporting information. After review and approval by FDA, the labeling would include statements in INDICATIONS AND USAGE, MICROBIOLOGY, ADVERSE REACTIONS, and possibly other sections in labeling (such as pre-clinical safety).

PhRMA recommends that the agency revise the draft guidance to also allow attainment of labeling in the MICROBIOLOGY section, without statements in the INDICATIONS AND USAGE section. This alternative scenario would enable a sponsor to submit an application based on *in vitro* activity against *B. anthracis*, as well as pharmacokinetic data showing drug exposures and tissue distribution consistent with likely *in vivo* activity against *B. anthracis*. Such data would merit inclusion of *B. anthracis* in the "*in vitro* only" portion of the MICROBIOLOGY section of labeling. This section of labeling would carry the standard statement that "*Drug X has been shown to be active in vitro against most strains of the following microorganisms; however, the clinical significance of these findings is unknown.*" Provision of such limited information in labeling is warranted in the interest of proactive preparation for the potential of a large-scale exposure or absence of access to approved therapies.

Page 7, Section C: The section on "Preclinical Toxicology Data" suggests that products have results for studies of toxicology in "at least two species" for 6 months of

drug exposure. In accordance with FDA's current standards, as well as ICH guidelines, an already marketed antibiotic drug product will typically have such results from two species (one rodent and one non-rodent), not more than two species as suggested by the language in the draft guidance.

Page 8, Section D (lines 334-335): The draft guidance suggests that *in vitro* testing of 30-50 isolates would be adequate. PhRMA hopes that FDA, industry, CDC, and others can collaborate to assure that part of this testing is done with clinical isolates obtained from patients with cutaneous or inhalation anthrax from the cases in the fall of 2001. Additionally, the government should facilitate either the availability of a standard set of appropriate isolates (i.e., a variety of genotypically different strains, etc.) for testing; or ideally, provide that set to one central laboratory that could conduct the testing by contract for sponsors.

The draft guidance does not mention the heterogeneity of the 30-50 isolates to be tested for susceptibility. Obviously, twenty genotypically different isolates would provide more valuable information than 50 (clonal) isolates from one or two geographical centers. The panel of *B. anthracis* isolates should contain standard strains (e.g., Vollum, Ames, Sterne), as well as proprietary exploratory medical and military isolates, including strains being considered for vaccine sourcing. This panel can be expanded by inclusion of naturally-occurring resistant isolates, as well as artificially manipulated isolates designed to test worst-case scenario bioterrorism strains (e.g., β-lactamase-producing strains, quinolone-resistant strains). A panel of drugs, representing each class of agent with wide human experience, should be used to benchmark the test agent in terms of *in vitro* susceptibility and resistance determination, thus avoiding the repetition of the same experiments with the same comparators for each drug's consideration as an anti-*B. anthracis* agent; this recommendation does not intend to remove controls, but to minimize the unnecessary risk of artificial manipulation and resistance development in the laboratory. This approach would also provide a side-by-side direct comparison of susceptibility patterns, and would quickly detect any unusual shift in susceptibility (such as a man-made bioterorrism derivative strain). A determination of bactericidal versus bacteriostatic activity of candidate drugs should be made by standard protocol, as there may be relevance in seeking and preferring a bactericidal agent for potential *B. anthracis* infection.

PhRMA disagrees with the statement in the draft guidance asking that this *in vitro* testing be done in "at least two to three laboratories". Very few laboratories are ready today to conduct such testing. Few new laboratories will acquire the capability due to increasing legal and regulatory actions (at the state and federal levels) to restrict and regulate lab-to-lab transfer of potential bioterrorism organisms. In PhRMA's view, data collected in a single laboratory (with appropriate methods, controls and quality assurance) on an appropriate set of isolates, as described above, should be acceptable to FDA. The preference for a single laboratory also recognizes the reality that, although

assays to assess resistance mechanisms are available, laboratories that conduct such studies on a regular basis are generally not equipped or approved from a biosafety perspective to handle this organism.

The draft guidance requests "studies to measure reciprocal cross-resistance". To PhRMA's knowledge, such studies were not required as part of the sNDA supporting ciprofloxacin, nor should it be mandated for subsequent drugs.

Regarding development of resistance studies (line 351), it is difficult even in active infections to correlate *in vitro* development of resistance studies with clinical outcome; it will be virtually impossible to do this in post exposure prophylaxis. This recommendation should be eliminated.

Identification of resistance mechanisms in resistant isolates would be very difficult as the specialized groups who perform such work are unlikely to have sufficient containment facilities to work on the strains. Additionally, *in vitro* resistance testing on *B. anthracis* strains is likely to result in the development of resistant isolates, thus posing further unnecessary risk. This should be downgraded to a suggestion.

All drugs approved for treatment of infections due to *B. anthracis* should be re-profiled, periodically, against a contemporary collection of B. anthracis strains, relying heavily on MIC results for fresh clinical isolates and, if available, drug-resistant strains (clinical and artificially attained) in order to assure updated susceptibility information on all drugs registered for treatment of *B. anthracis*. Such re-profiling should be done if sufficient numbers of new clinical isolates become available from patients exposed to this bacterium in the United States. Such re-profiling may best be done by a central laboratory with demonstrated expertise in standardized testing of *B. anthracis*.

Page 8, Section E: The draft guidance requests at least 10 monkeys per group (line 381); is there any specific gender required? Friedlander's article does not mention if males and/or females need to be used (i.e., is the 10 animals/group really 5/sex/group?). This should be clarified. Additionally, the FDA should consider providing guidance on the strains to be included in animal model studies.

Recommendations for dosing in the monkey studies should be re-evaluated. The draft guidance requests that (a) the animal dose should provide systemic exposure comparable to the anticipated human exposure and (b) the drug regimen (e.g., QD, BID) should be the same as anticipated in humans. These two requirements may be mutually exclusive, depending on the relative pharmacokinetic properties in monkeys and humans.

The draft guidance recommends assessment of drugs with the rhesus monkey model by Friedlander. It also states that applicants "should also consider developing models

using small animals (e.g., guinea pigs)". The draft guidance suggests that the small animal models may be useful, but only in addition to the monkey model. Because of the very limited laboratories able to use this monkey model, the requirement for efficacy testing in the monkey model is currently the primary hindrance to approval of alternative therapies for inhalational anthrax. There is no mention of other rodent models, although published information suggests that murine models may be predictive. Murine model infections have been well accepted in the past to demonstrate efficacy of new agents for many disease states. Mice are certainly cheaper, easier to house, and more amenable to comparative studies when large numbers of animals are needed to show statistical significance. There are also animal welfare considerations that would promote the use of rodents rather than non-human primates when possible. We encourage the Agency to state their openness to an appropriate murine or other small animal model.

Page 9, Section E, last summary bullet: The guidance states that "histopathology data on animals that die during the study should be recorded". PhRMA recommends that the Agency add the clarification, consistent with the paper by Friedlander *et al.*, that the expectation is that the following organs are subject to histopathologic examination: blood, brain, liver, lung, and spleen.

Page 10, Section F: The requirement that PK data for pregnant women be submitted should be made a suggestion rather than a requirement.

Page 11, Section H. Paragraph 1: The draft guidance states that "there should be sufficient data on prolonged use of the drug in large numbers of patients". We believe that this expectation may represent a significant barrier to products that may have a legitimate role in this important indication. The agency recognizes that antibiotics are used mainly for limited durations and, thus, data on prolonged durations of use (e.g., 60 days or longer) will typically be limited. An antibiotic with impressive *in vitro* activity against *B. anthracis* and in an animal model should, in our view, be a candidate for this indication, despite a limited database on prolonged duration of use. The Agency should clarify that the assessment of approvability of an application for this indication will be based on the totality of evidence on the drug, with weighing of the benefits versus risks (including any limitation associated with a limited database on prolonged use).

Page 12, Section I, Statistics: Will the Agency be specific as to what they want as the primary efficacy endpoint for the monkey model? Is it post-exposure survival?

Page 12, Section L, Postapproval Commitments: It is noteworthy that FDA anticipates granting Accelerated Approval for this indication, with the requirement that sponsors commit to collect "*confirmatory clinical data . . . in the event of an accidental or intentional exposure to aerosolized B. anthracis*". Systematic collection and analysis

of such data (using an approach that resembles the approach to confirmatory clinical trials for other drugs that have received accelerated approval) will be, frankly, impossible. Further, PhRMA anticipates that it will be extremely difficult and largely impractical to even collect non-comparative Case Report information during a period of accidental or intentional exposure. With respect to this topic, little information is available in the FOI documents on FDA's accelerated approval of Cipro Tablets. FDA should provide more details on the confirmatory program that they view as necessary and also practical for implementation. Absent such information, the uncertainty and potentially long-term nature of this postapproval commitment may impede development of such products. It may well be that collection of any data following exposure in the United States can only be done, practically, by CDC in collaboration with other governmental agencies. Additionally, promotional material for this indication should require clearance by the Agency only before its initial use.

Page 13, Section VI. Summary: What constitutes an "adequate number of isolates" should be specified.

Additional Suggestion: The bioterrorism threat in the United States is very concerning and, unfortunately, real. The multiple cases of *Bacillus anthracis* in late 2001 made the threat a reality in multiple states (1). Clearly, *B. anthracis* is not the only microorganism that appeals to terrorists for utility as a weapon. Dr. Franz, Dr. Friedlander, and colleagues at the US Army Medical Research Institute of Infectious Diseases have provided recent informative reviews of various biological warfare pathogens, including *B. anthracis* (anthrax), *Yersinia pestis* (plague), *Brucellae* (bruellosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), and *Clostridiuum botulinum* (botulinum toxins) (see references 2-3). Based on the keen awareness of this issue within PhRMA companies, and on our knowledge that success in combating such pathogens requires a collaborative effort between the government and industry, the FDA should use this opportunity and follow-up with an issuance of a broader draft guidance document, e.g., "Draft Guidance Document on Developing Drugs for Bioterrorism Indications". Such a broader draft guidance document would assist government and industry in planning for multiple threats, including anthrax. PhRMA anticipates that most of what the agency would require for a Supplemental Application for any of the bioterrorism indications would be identical in principle (i.e., toxicology data, microbiology data, evidence of efficacy in an appropriate animal model, clinical pharmacology data, evidence of efficacy in other indications, information on safety from various durations of treatment, and any available data on various patient subpopulations). Issuing a draft guidance to address the broad principles of bioterrorism indications, rather than issuing a separate guidance for each individual indication, may be a more efficient use of agency and industry resources, given the recent past and the current threats.

Summary

In summary, this draft guidance should stimulate progress and facilitate registration of products for post-exposure treatment of inhalation anthrax. PhRMA has reservations that the document, in its current format, will accomplish that goal. A major problem is the difficulty of conducting rhesus monkey studies and the lack of alternative small animal models.

PhRMA suggests that the FDA ensure the following to help address this situation:

- Facilitate government inter-agency cooperation in setting up one multi-armed rhesus monkey study for currently marketed products that are most likely to be efficacious.
- Facilitate the development of small animal models by (1) conducting studies in federal laboratories, (2) funding studies in independent research laboratories, and (3) working with PhRMA to initiate cooperative industry studies.
- Develop a panel (in conjunction with CDC, NCCLS and USAMRIID) of *B. anthracis* isolates for *in vitro* MIC testing. These isolates should be made available to either a government or an independent laboratory/laboratories that could then perform the *in vitro* work needed for registration.
- Rapidly progress consensus (in conjunction with CDC, NCCLS and USAMRIID) on *in vitro* MIC methodology for *B. anthracis*.

On behalf of PhRMA and the Antimicrobial Working Group, PhRMA appreciates the opportunity to comment on this draft guidance document and would be pleased to discuss any of our comments with the FDA.

Sincerely,

References

1. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon, 2002. Updated recommendations for management. *JAMA* 287: 2236-2252 (2002).

2. Franz DR. Jahrling PB, Friedlander AM, McClain DJ. Hoover DL, Bryne WR, Pavlin JA, Christopher GW, Eitzen EM. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA* 278: 399-411 (1997).

3. Franz DR. Jahrling PB, McClain DJ, Hoover DL, Bryne WR, Pavlin JA, Christopher GW, Cieslak TJ, Friedlander AM, Eitzen EM. Clinical recognition and management of patients exposed to biological warfare agents. *Clinics in Laboratory Medicine* 21: 435-473 (2001).